REMARKS

Claims 1-22 are pending. Claims 6, 9 and 15-17 stand withdrawn as being directed to a non-elected invention. Accordingly, claims 1-5, 7, 8, 10-14 and 18-22 are under examination. Claims 1 and 19 have been amended. Support for the amendment can be found throughout the application as filed and at, for example, the claims as originally filed, the Brief Description of the Drawings, Example I, Table I and in paragraphs 0044. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Applicants acknowledge that claims 21 and 22 are free of prior art.

Rejections Under 35 U.S.C. § 101

Claims 1-5, 7, 8, 10-14 and 18-22 stand rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. The Examiner alleges that the claims are directed to an abstract idea. Applicants respectfully traverse.

In re Bilski, 545 F.3d 943, (Fed. Cir. 2008) held that a process claim defines patentable subject matter if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article to a different state or thing." *Id.* at 954, 956 (*citing Gottschalk v. Benson*, 409 U.S. 63, 70 (1972)). Applicants respectfully submit that the claimed invention meets either or both branches of this "machine-or-transformation" test articulated by the *Bilski* court.

The Examiner asserts that the claimed invention fails to physically transform an article or physical object to a different state or thing allegedly because the claimed *in silico* method steps are directed to mental processes.

The question before the *Bilski* court was whether the claimed process recited a fundamental principle and, if so, whether it would pre-empt substantially all uses of that fundamental principle if allowed (see *Bilski*, fn 5 at 952, defining a fundamental principle to mean laws of nature, natural phenomena and abstract ideas). *Id.* at 954. The claims in issue were directed to a business method of hedging risk in the field of commodities trading. *Id.* at 949. The court held that the claimed method was not directed patent-eligible subject matter because there was no transformation of an article into a different state or thing.

In arriving at this conclusion, the court analyzed Federal Circuit precedent with respect to the transformation test to clarify "what sorts of things constitute 'articles' such that their transformation is sufficient to impart patent-eligibility under § 101." *Id* at 962. Recognizing that

"[t]he raw materials of many information-age processes . . . are electronic signals and electronically manipulated data" and addressing "[w]hich, if any, of these processes qualify as a transformation or reduction of an article into a different state or thing" (*Id.* at 962) the court concluded:

> So long as the claimed process is limited to a practical application of a fundamental principle to transform specific data, and the claim is limited to a visual depiction that represents specific physical objects or substances, there is no danger that the scope of the claim would wholly pre-empt all uses of the principle.

Id. at 963 (*emphasis added*).

Relying on the mixed results in *Abele*, (*In re Abele*, 684 F.2d 902 (CCPA 1982), the *Bilski* court noted that a claim directed to a process of graphically displaying variances of data from average values was held unpatentable because the claim did not specify any particular type or nature of data, how or where the data was obtained or what it represented. In contrast, a dependent claim directed to X-ray attenuation data produced by computer tomography was found to be statutory subject matter because:

> This data clearly represented physical and tangible objects, namely the structure of bones, organs, and other body tissues. Thus, the transformation of that raw data into a particular visual depiction of a physical object on a display was sufficient to render that more narrowly-claimed process patent-eligible.

Bilski 545 F.3d at 962-63 (*citing Abele*, 684 F.2d at 908-09).

Bilski further clarified that electronic transformation of data is sufficient to render a process claim patent eligible subject matter when the court stated:

> We further note for clarity that the electronic transformation of the data itself into a visual depiction in *Abele* was sufficient; the claim was not required to involve any transformation of the underlying physical object that the data represented. We believe this is faithful to the concern the Supreme Court articulated as the basis for the machine-or-transformation test, namely the prevention of pre-emption of fundamental principles.

Id. at 963 (*emphasis added*).

Thus, *Bilski* found that, when properly applied to electronic signals and electronically manipulated data, the transformation branch of the machine-or-transformation test does not require transformation of an underlying physical object the data may represent. Rather, the

transformation branch is satisfied when electronic data is transformed into a visual depiction. Applicants respectfully point out that the claimed invention satisfies this branch of the test.

Claims 1 and 19 are directed to a method for determining candidates for gene deletions using a model of a metabolic network associated with an organism. The model includes a plurality of metabolic reactions defining metabolite relationships. The method includes solving a linear optimization problem of objective functions of the plurality of metabolic reactions and providing a visual output of at least one candidate gene deletion to a user.

Although not required, Applicants point out that the underlying objects represented by the data in the claimed *in silico* method correspond to physical objects or substances in biochemical reaction networks within a living cell. For example, the data represents enzymes, substrates, products and co-factors and are physical objects like the bones, organs and other body tissues represented by the X-ray computer tomography data under the *Bilski* reasoning. This data is electronically represented in a computer in the claimed *in silico* method. Computational methods disclosed in the specification and recited in the claim are applied to the claimed electronic representation to solve the optimization problem applied to the metabolic network and the results are visually displayed. Hence, the claimed invention represents underlying physical components of a living cell in electronic data, manipulates that electronic data to generate an optimized representation of the physical components and transforms that optimized representation by providing a visual output of the candidate gene deletions to a user. Therefore, the claim "transforms specific data . . . to a visual depiction that represents specific physical objects or substances [and] there is no danger that the scope of the claim would wholly pre-empt all uses of the principle. *Bilski*, 545 F.3d at 963 (*supra*). Accordingly, claims 1 and 19 are patent-eligible subject matter because they satisfy the transformation branch of the machine-or-transformation test articulated by the Supreme Court and clarified in *Bilski*. Applicants respectfully request that this ground of rejection be withdrawn.

Although not required to satisfy both alternatives of the machine-or-transformation test, nevertheless, independent claims 1 and 19 of the subject invention also satisfies the alternative machine implementation branch of the test.

The Examiner restricts the machine implementation branch, requiring tying the claimed process to a particular machine or apparatus, to further exclude "insignificant pre-solution and post-solution activity." Such a requirement does not appear to be articulated by the *Bilski* court

with respect to machine implementation branch of a process claim. The *Bilski* court explicitly acknowledged that the question of whether a fundamental principle, when tied to a particular machine, would render the claims statutory patentable under § 101 was not in issue in *Bilski*.

> As to machine implementation, Applicants themselves admit that the language of claim 1 does not limit any process step to any specific machine or apparatus. As a result, issues specific to the machine implementation part of the test are not before us today.

Id. at 962 (*emphasis added*).

Thus, any discussion in *Bilski* referring to an exclusion of allegedly insignificant pre- or post-solution activity is dicta and inapplicable to a machine implementation analysis of the claimed invention. With respect to the Examiner's reliance on *Comiskey*, Applicant's submit that the output is not insignificant post-solution activity.

Claims 1 and 19 recite that the claimed metabolic network associated with an organism is a model and that a visual output is provided to a user. Claim 19 expressly recites a computer-based method. Thus, claims 1 and 19 and their dependents satisfy the machine-or-transformation test because the method for determining candidates for gene deletions is implemented by a particular machine. Moreover, assuming *arguendo* that insignificant extra solution activity does not make non-statutory subject matter patent-eligible, Applicants' visual output is not insignificant. The claims are directed to a method for determining candidates for gene deletions or, with respect to claims 21 and 22, gene deletions and additions. If the claimed method failed to provide an output of the candidates the user would not be able to modify a model or a living cell to the predicted optimized version because the user would not know what biochemical reactions in the network to change. Hence, the output in the claimed method in not insignificant.

In light of the above remarks and amendments, Applicants submit that the claimed invention falls within statutory patentable subject matter. The claims meet the transformation branch of the machine-or-transformation test articulated in *Bilski* because it transforms electronic data representing specific physical objects to a visual depiction. While not required, the claims also meet the machine implementation branch of the test because the claimed method is tied to a computer. Moreover, machine implementation of the claimed method is not patent-eligible due to an insignificant extra solution activity because the generated output provides the user with the

modifications that produce optimized properties of the metabolic network. Accordingly, Applicants respectfully request that this ground of rejection be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1, 5, 7, 8, 10, 11, 13, 14, 19 and 20 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *AIChE J.* 42:1277-1292 (1996), in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000). Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis et al. in combination with Bhaskar et al.

Claim 1 is directed to a method for determining candidates for gene deletions using a model of a metabolic network associated with an organism, the model comprising a plurality of metabolic reactions defining metabolite relationships. The method includes forming a linear optimization problem that couples at least one cellular objective function with at least one bioengineering objective function and solving the linear optimization problem to yield at least one candidate gene deletion. Claim 19 is directed to a computer-based method for determining candidates for gene deletions using a model of a metabolic network associated with an organism, the model comprising a plurality of metabolic reactions defining metabolite relationships. The method includes forming a linear optimization problem that quantifies at least one cellular objective function as an aggregate reaction flux and couples it with at least one bioengineering objective function and solving the linear optimization problem to yield at least one candidate gene deletion.

The Examiner appears to allege that Applicants arguments are not persuasive because the purported descriptions to regulatory control in Hatzimanikatis et al. are analogous to Applicants identification of gene deletions. Further, the Examiner also appears to allege that Applicants showing of teaching away lacks persuasiveness because Hatzimanikatis et al. suggests that growth and metabolite production are linked.

Applicants respectfully point out that whether the purported descriptions to regulatory controls are analogous to identification of gene deletions is immaterial. Rather, Applicants pointed out in their previous response that the purported descriptions cited by the Examiner fail to teach or suggest a method for determining candidates for gene deletions by forming a linear optimization problem that couples at least one cellular objective function with at least one bioengineering function and solving the linear optimization problem to yield at least one

candidate gene deletion. At most, the cited descriptions instead are directed to design of metabolic reaction networks through modification of regulatory structures without a suggestion or motivation to combine solving both a cellular objective function and a metabolic function. There is no showing of a suggestion or motivation to couple the two claimed objective functions.

Similarly, the Examiner's conclusion that Hatzimanikatis et al. fail to teach away also is unfounded. Without admission that the Examiner's rationale is correct, the conclusion that growth and metabolite production can be linked in an organism has been long established. In contrast, coupling a cellular objective function with a bioengineering function in a metabolic model using a linear optimization problem has not. Therefore, as with the initial showing above, here too, the Office fails to make a showing of a suggestion or motivation to couple the two claimed objective functions. To establish a *prima facie* case of obviousness, the Examiner must show that one skilled in the art would have arrived at the claimed invention with a reasonable expectation of success given the cited art. Applicants contend that such showing is absent. Applicants reiterate and reassert their arguments of record.

The Supreme Court in *KSR* stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l. Co. v. Teleflex, Inc., et al.*, 127 S. Ct. 1727 (2007). The Supreme Court noted that inventions in most, if not all, instances rely upon building blocks "long since uncovered." Thus, claimed discoveries will generally be combinations of what is already known. *KSR* requires that an Examiner provide "some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Id.* at 1741. An Examiner must "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does," *Id.* Furthermore, the Examiner must include an explanation of "the effects of demands known to the design community or present in the marketplace" and "the background knowledge possessed by a person having ordinary skill in the art." *Id.* It is respectfully submitted that the current Office Action falls short of providing the analysis described by the Supreme Court in *KSR* which would show that one skilled in the art would have arrived at the invention as claimed.

In this regard, Hatzimanikatis et al. appear to describe the use of mixed-integer linear optimization to arrive at different solutions to an optimization problem. Similarly, Bhaska et al. appear to describe a review of multi-objective or dual optimization problems, none of which

couple a cellular objective function with a bioengineering objective function. Similarly, neither reference appears to teach or suggest coupling a cellular objective function and a bioengineering function. Hence, each reference at most appears to describe solving an optimization problem.

For example, Hatzimanikatis et al. postulate the number of regulatory loops in a metabolic pathway and then solve each hypothesis by mathematical optimization to identify how to increase function (page 1279, col. 1, first para. under "Problem Statement). Problem 1 describes the solution to the mixed-integer linear optimization problem (MILP) for the question which of the existing regulatory loops should be inactivated and which should be the associated changes in the enzyme expression levels to maximize phenylalanine selectivity (page 1284, col. 1). Problem 2 describes the solution to the optimization problem which maximizes the phenylalanine selectivity given four questions regarding inhibitors and enzyme expression (page 1285, col. 2). Problem 3 describes the solution to the optimization problem which maximizes the phenylalanine selectivity given four questions regarding activators and enzyme expression (page 1287, col. 1). Whereas Problem 4 describes the solution to the optimization problem which maximizes the phenylalanine selectivity given five questions regarding regulation and enzyme expression (page 1287, col. 2).

In postulating different regulating loops and identifying solutions to each optimization problem Hatzimanikatis et al. fail to provide any teaching or suggestion to couple a cellular objective function with a bioengineering objective function. Rather, Hatzimanikatis et al. at most describe the solutions to four different mixed-integer linear optimization problems (e.g., Problems 1-4). Bhaskar et al. similarly fail to provide such a teaching or suggestion because Bhaskar et al. is merely directed to dual theory and fails to provide any insights into combining diverse objective functions such as cellular and bioengineering objective functions. Bhaskar et al. describe the various techniques for generating Pareto sets, which include the lexicographic approach, Parametric approach, ε-Constraint approach and Goal Programming. There is no teaching or suggestion of a cellular or metabolic objective function much less the coupling of these two functions.

Absent some teaching or suggestion of coupling a cellular objective function with a bioengineering objective function the cited combination cannot render the invention as claimed obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 1, 2, 4 and 18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Bhaskar et al., *supra*, and further in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999). Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis et al., alone or in combination with Bhaskar et al. and/or Yang et al.

As discussed above, Applicants respectfully submit that Hatzimanikatis et al. in combination with Bhaskar et al. do not teach or suggest the claimed methods. Furthermore, Applicants respectfully submit that Yang et al. does not cure the deficiencies of Hatzimanikatis et al., alone or in combination with Bhaskar et al. Yang et al., at best, describe the use of metabolic flux analysis in an *Escherichia coli* strain deficient in the acetate production pathway. However, as discussed previously on the record, Yang et al. does not discuss forming an optimization problem that couples at least one cellular objective function with a bioengineering objective function. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis et al., in combination with Bhaskar et al. and/or Yang et al. Therefore, Applicants respectfully request that this rejection be withdrawn.

Claims 1, 5, 7, 8, 10-14, 19 and 20 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Burgard et al., *Biotechnol. Bioeng.* 74:364-375 (2001), in view of Bhaskar et al., *supra*. Applicants respectfully submit that the claimed methods are unobvious over Burgard et al., in view of Bhaskar et al..

Applicants respectfully maintain that Burgard et al. in combination with Bhaskar et al. do not teach or suggest the claimed methods of determining candidates for gene deletions by forming a linear optimization problem that couples at least one cellular objective function with at least one bioengineering objective function. Burgard et al. discuss a gene knockout study that explores what is the smallest gene set capable of maximizing biomass production on glucose substrate and what is the maximum number of gene deletions from this set that still maintain a specified level of biomass production. Separately, Burgard et al. discuss identifying mathematically optimal reaction pathways to recombine into the *E. coli* metabolic network to optimize amino acid formation for growth on glucose and acetate.

Burgard et al. states on page 365, column 2, 2nd complete paragraph,

> In this work, we examine how stoichiometric boundaries of cellular performance expand or contract in the presence of multiple gene additions or deletions. A FBA model of the cellular metabolism of *E. coli* is constructed incorporating the reaction pathways provided by Pramanik and Keasling (1997), along with modifications suggested by Karp et al. (1999) based on more recent data. The modifications are either small molecule corrections based on more recent metabolic information or the removal of certain pathways now known to be absent from the *E. coli* genotype. [*emphasis added*]

Thus, it is clear that Burgard et al. is describing in this context the correction of the Pramanik and Keasling reaction pathways for *E. coli* by making small molecule corrections and excluding pathways "now known to be absent from the *E. coli* genotype." Burgard et al. reiterate this under their description of "*Escherichia coli* Stoichiometric Models" (p. 366, col. 2, 2nd para.).

> The stoichiometric *E. coli* model used in this study employs 178 irreversible, 111 reversible, and 12 transport reactions compiled largely from the model published by Pramanik and Keasling (1997). The modifications to the Pramanik and Keasling stoichiometric matrix are given in Table 1. They are primarily small molecule corrections (e.g., ATP in place of GTP for succinate thiokinase) or the removal of reactions now known to be absent from *E. coli* based on more recent data (Karp et al., 1999). Note that similar changes were also independently included in the most recently published *E. coli* model of Edwards and Palsson (2000a). [*emphasis added*]

Similar to the passage above it is clear that these modifications are merely corrections to the Pramanik and Keasling reaction pathways for *E. coli* based on more recent information. However, these passages in Burgard et al. in no way teach or suggest coupling a cellular objective function with a bioengineering function as asserted in the Office Action. Moreover, it is clear from the description in Burgard et al. that the "stoichiometric *E. coli* model" is the starting model from which they model gene deletions and additions.

> Given a stoichiometric model of *E. coli* metabolism and the Universal stoichiometric matrix encompassing reactions occurring in multiple species, the goal of this section is to formulate a mathematical model that 1) captures cellular robustness in the presence of multiple gene deletions, and 2) identifies additional genes from the Universal dataset having the most profound effect on improving a given metabolic objective. [emphasis added]

Thus, it is clear that the "removal of certain pathways" from the Pramanik and Keasling reaction pathways for *E. coli* is to provide a more accurate starting *E. coli* model for their

mathematical modeling and occurs prior to their mathematical modeling. However, such a description cannot be considered to provide a teaching of coupling a cellular objective function with a bioengineering function

The Office Action acknowledges on page 12 that "Burgard et al. do not teach the generation of a bilevel optimization problem or the coupling of cellular and bioengineering objective functions." Furthermore, as discussed above, Burgard et al. describe the determination of a set of gene deletions that provides the smallest gene set to achieve a desired level of growth and the determination of gene additions to produce a desired product as separate goals achieved using mathematical calculations for optimizing each goal. The fact that Burgard et al. separately describes the goal of optimizing a bioengineering objective by determining gene additions or optimizing a cellular objective by determining the smallest gene set that permits the cell to attain specified levels of biomass production in no way provides one skilled in the art with the desirability of modifying the description in Burgard et al. with the multi-objective optimization of Bhaskar et al. to form a linear optimization problem that couples a cellular objective function with a bioengineering function and to solve the linear optimization problem to yield at least one candidate gene deletion.

Therefore, Applicants respectfully submit that the claimed methods are unobvious over Burgard et al. in combination with Bhaskar et al. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claims 1-4 and 18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Burgard et al., *supra*, in view of Bhaskar et al., *supra*, and further in view of Yang et al., *supra*. Applicants respectfully submit that the claimed methods are unobvious over Burgard et al. in combination with Bhaskar et al. and/or Yang et al.

As discussed above, Applicants respectfully submit that Burgard et al., alone or in combination with Bhaskar et al. do not teach or suggest the claimed methods. Furthermore, Applicants respectfully submit that Yang et al. does not cure the deficiencies of Burgard et al. and Bhaskar et al. Yang et al., at best, describes the use of metabolic flux analysis in an *E. coli* strain deficient in the acetate production pathway. However, as discussed previously, Yang et al. does not discuss forming an optimization problem that couples at least one cellular objective function with a bioengineering objective function. Accordingly, Applicants respectfully submit

that the claimed methods are unobvious over Burgard et al. in combination with Bhaskar et al. and/or Yang et al. Therefore, Applicants respectfully request that this rejection be withdrawn.

Conclusion

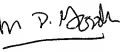
In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

This is a request under the provision of 37 CFR § 1.136(a) to extend the period for filing a response in the above-identified application for three months from February 25, 2009 to May 26, 2009. Applicant is a small entity; therefore, please charge Deposit Account No. 26-0084 in the amount of $555.00 to cover the cost of the three-month extension. Any deficiency or overpayment should be charged or credited to Deposit Account 26-0084.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



JOHN D. GOODHUE, Reg. No. 47,603
McKEE, VOORHEES & SEASE, P.L.C.
801 Grand Avenue, Suite 3200
Des Moines, Iowa 50309-2721
Phone No: (515) 288-3667
Fax No: (515) 288-1338
CUSTOMER NO: 27407

Attorneys of Record

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